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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,387	01/14/2005	Reiner Luttmann	SARTORIUS-12	2344

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EXAMINER	
HOBBS, MICHAEL L	
ART UNIT	PAPER NUMBER
4151	
MAIL DATE	DELIVERY MODE
12/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,387	LUTTMANN ET AL.	
	Examiner	Art Unit	
	Michael L. Hobbs	4151	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Drawings

1. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they do not include the following reference sign(s) mentioned in the description: the third feed receptacle element 4 which is first encountered on page 9 line 8 is not listed on Figures 1 and 3. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

2. The disclosure is objected to because of the following informalities: on page 4 line 13, applicant refers to the yeast "Pichie pastoris" instead of Pichia pastoris as the yeast used in the production of recombinant proteins. The examiner assumes that applicant meant to use Pichia pastoris instead of "Pichie pastoris".

Appropriate correction is required.

Claim Objections

3. Claim 11 is objected to because of the following informalities: on line 2, applicant refers to the yeast "Pichie pastoris" instead of Pichia pastoris as the yeast used in the production of recombinant proteins. The examiner assumes that the yeast referred to in this claim is Pichia pastoris and not "Pichie pastoris". Claims 4 and 15 are objected to because of the following informalities: on line 2 of claim 4 and claim 15, applicant recites the "process" when referring to the method of claim 1. Apparently, "the method" should be indicated in these claims instead of "the process" and the examiner assumes that is what the applicant refers to for these claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 6 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 6 recites "the induction of product formation" in the second line of the claim and probably refers to the production of recombinant proteins or "valuable products". Also, it is unclear how the "induction of product formation" relates to the production of recombinant proteins. There is insufficient antecedent basis for the limitations in the claim.

7. Regarding claim 17, the phrase "essentially comprising" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

8. Therefore, appropriate clarifications and/or corrections are required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 2, 4, 8-10, 15-18 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Kopf (U.S. 6,214,574).

11. For claim 1, Kopf teaches feeding a medium to a bioreactor or a tangential growth device (col. 15 lines 65-67) and **subject to fermentation** or cell growth (Abstract) in which the cells are **harvested from a cross-flow filtration unit** or a membrane (col. 17 lines 11-14, 38-42) with the **residues** or retentate supplied back to the bioreactor (col. 17 lines 7-11). Also, other substances that can increase the yield of the bioreactor can be supplied in a **controlled manner** (col. 16 lines 24-27) and the **retentate and permeate** can be harvested in a **controlled manner** (col. 16 lines 50-51). The **fermentation process** or cell growth and **filtration** can be **regulated** by the way of a monitoring system or **control unit** (col. 17 lines 2-3). Regarding claim 2, it is inherent in the steps of Kopf to be able to **clean and sterilize the system in situ** where

this process is **controlled by the control unit** (Abstract). For claim 4, that the **process proceeds in a sequential and integrated manner** is inherent to the teachings of Kopf. Regarding claim 8, Kopf mentions the step of removing a **cell-free harvest** from the **bioreactor** or growth device during the harvesting phase (col. 16 lines 41-42, Fig. 15 elements 144, 155, 154). Whereas for claim 9, Kopf teaches **harvesting the cell mass in the retentate** or removing spent medium by employing filters and **refreshing the medium by feeding new medium into the system** from a nutrient tank (col. 18 lines 19-23, col. 17 lines 32-35, Fig. 3 element 170). With regards to claim 10, the valve for the permeate (Fig. 15 element 172) is closed when not harvesting and the **retentate stream flows** within the mass transfer system (col. 17 lines 42-44) Also, for claim 15, the **process** being **conducted in a continuous and integrated manner** Kopf teaches culturing the cells continuously on a micro-bead substrate and for claim 16, the **product and cell harvesting phases proceed in** parallel are inherent to the teachings of Kopf.

12. Regarding claim 17, Kopf teaches having a tangential flow growth device that reads on a **bioreactor** (col. 15 lines 65-67, Fig. 15 element 144) with a main reservoir or a **first feed** receptacle “upstream” from the reactor (col. 17 lines 1-2, Fig. 15 element 163) where the **bioreactor** is connected to a sterile barrier tangential flow membrane (**cross-flow filter**) (col. 17 lines 11-14, Fig. 15 element 164). Also, the permeate line from the filter is connected to a collection reservoir or **first harvest tank** (col. 18 lines 45-48, Fig. 15 element 174) and the flow membrane is connected to the growth device by a tube or **retentate line** (col. 17 lines 9-11, Fig. 15 element 161). An auxiliary reservoir or **second feed receptacle** can hold substances to increase the yield

(**inducing substance**) within the growth device (col. 16 lines 24-27, Fig. 15 element 148) and another auxiliary reservoir or a **second harvest receptacle** connected to the growth device can be used to concentrate or separate cellular by-products by way of a tube (col. 16 lines 50-51, Fig. 15 elements 156 & 158). Also, Kopf includes a monitoring system or **control unit** that may be implemented by computerization to adjust system conditions (col. 17 lines 2-3).

13. Regarding claim 18, Kopf teaches a monitoring system or **control unit** that adjusts system conditions such as **concentration of the inducing substance** by monitoring chambers (Fig. 15 element 162) that read on an **analytical system** that controls the pump (Fig. 15 element 152) from the auxiliary reservoir (Fig. 15 element 148) to administer the yield increasing substance (col. 17 lines 2-5).

14. With regards to claim 20, the monitoring system and chambers of Kopf can measure the conditions within the growth device such as cell concentration and can control the pump to the first auxiliary reservoir (col. 17 lines 50-53, Fig. 15 elements 174 & 175).

15. Therefore, Kopf meets all the limitations of claims 1, 2, 4, 8-10, 15-18 and 20.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 3, 5-7, 11-14, 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopf (U.S. 6,214,574) in view of Cornelissen et al. (CAB8-Computer Applications in Biotechnology, June 25-27, 2001).

20. With regards to claim 3, Kopf teaches the step of obtaining a **cell-free harvest in the permeate and a cell-contaminated harvest in the retentate** obtained from the filter where the permeate containing products such as hormones or the HIV virus goes to an auxiliary reservoir and the retentate remains in the mass transfer system (col. 17 lines 50-53, col. 18 lines 45-49). Regarding claim 6, Kopf teaches that during **the**

production phase, the induction of product formation can be assisted by adding yield enhancing or **inducing substances** to increase the overall yield within the growth device (col. 17 lines 2-5).

21. For claim 3, Kopf remains silent as to the step of producing **valuable products** where those products are **recombinant proteins.** Kopf does not teach the steps for claim 5 where the supplied cells to the bioreactor **adapt** (adjust) **to the medium** and that the cells are **propagated at a constant growth rate**. Regarding claim 7, Kopf does not teach the step of **controlling the concentration of the inducing substance is measured by a flow diffusion analysis (FDA)** and **regulated by a second feed receptacle**. For claims 8 and 9, Kopf does not mention that during the harvesting phase of the bioreactor that **a part of said reactor is harvested cell free** and that **the cell mass in the retentate is harvested** which is **followed by a medium refreshing phase**. With regards to claims 11 and 12, Kopf does not teach the steps of **producing the recombinant DNA with the yeast Pichia pastoris (P. pastoris)** and that **methanol is used as the inducing substance** added to the bioreactor. For claims 13 and 14, Kopf does not teach the steps of **maintaining the methanol concentration at a constant level** and that the step of **feeding glycerol in either the batch or producing phase** to increase production. For claims 19 and 20, Kopf does not teach **monitoring the system with a flow diffusion analysis or FDA** and for claim 21, that **a third regulator is connected to the feed pipe by way of a weighing device**.

22. For claim 3, Cornelissen teaches the step where the **valuable product** is recombinant proteins (Abstract). Regarding the method of producing biotechnologically

valuable products as in claim 5, Cornelissen teaches that the cells adapt to the medium and that the cells are propagated at a constant growth rate, μ, for the batch phase (page 3 sections 3 and 4, Fig. 2). At the time of the invention, it would have been obvious to one of ordinary skill in the art to employ the steps of producing recombinant proteins of Cornelissen within the teachings of Kopf in order to separate and control the growth of the desired product. The suggestion for doing so at the time would have been to implement steps that are reproducible and enable stable production conditions (page 6 section 8).

23. For claim 7, Cornelissen teaches the step of using a flow diffusion analysis (FDA) to regulate a second feed receptacle (page 3 section 4, Fig. 3). At the time of the invention, it would have been obvious to one of ordinary skill in the art to employ the step of using a flow diffusion analysis device within the teachings of Kopf in order to control the flow of nutrient or medium to the bioreactor. The suggestion for doing so at the time would have been to prevent possible fouling of the filter (page 3 section 4).

24. Regarding claim 11, Cornelissen teaches the step where the yeast used to produce the **recombinant DNA** is Pichia pastoris (Abstract) (claim 11) and for claim 12, Cornelissen teaches the step where the inducing substance is methanol (page 3 section 4, Fig. 1 & Fig. 3). Therefore, at the time of the invention, it would have been obvious to one of ordinary skill in the art to employ the recombinant DNA production of Cornelissen within the teachings of Kopf in order to produce and control the amount of product produced. The suggestion at the time would have been to use P. pastoris to produce

the recombinant DNA and methanol to control the growth rate within the bioreactor for the proper convolution of the recombinant products (page 1 section2).

25. Regarding claims 13 and 14, Cornelissen teaches maintaining the methanol level at a constant level and that glycerol is fed to the bioreactor (page 3 sections 3 & 4, Fig. 3). At the time of the invention, it would have been obvious to one of ordinary skill in the art to employ the flow and production controls of Cornelissen within the teachings of Kopf to optimize the production of recombinant DNA. The suggestion for doing so would have been to precisely control the amount of product produced and the particular production stage when said product will be harvested.

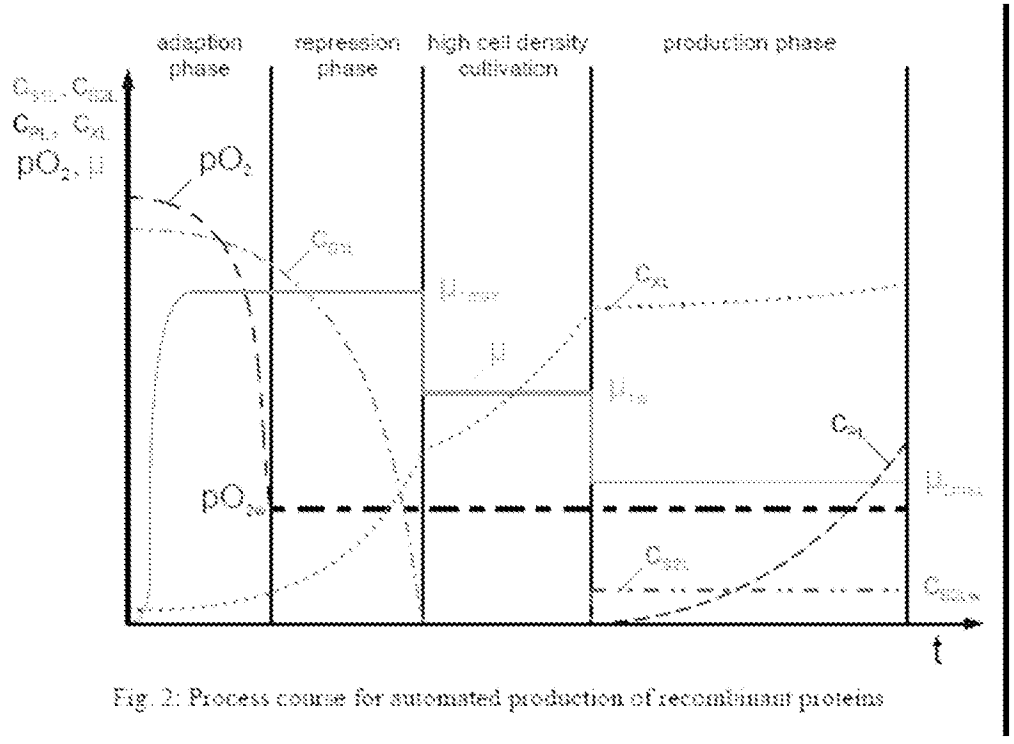

Fig. 2: Process course for automated production of recombinant proteins

Figure 1: Automated production of recombinant proteins (Cornelissen et al.)

26. Regarding the device for producing biotechnological valuable products as in claim 19, Cornelissen teaches an analytical system in the form of a flow diffusion analysis (FDA) (page 3 section 4 lines 18-19, Fig. 3). For claim 21, the weight control of Cornelissen is connected to the bioreactor and to the feed pump for the product harvest tank, but is fully capable of being connected to the feed pump and regulating flow of medium to the bioreactor. At the time of invention, it would have been obvious to one of ordinary skill in the art to employ the FDA and weight control for the feed pump within the teachings of Kopf in order to automate the cell growth device. The suggestion for doing so would have been to prevent equipment failure and minimize the loss of product due to said equipment failure during the culturing process.

Conclusion

27. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. This pertinent art includes Guinn et al. (U.S. 4,889,812), which is a bioreactor that includes a recirculation system for the harvest material and the nutrient media that is feed to the bioreactor. Also, the polypeptide production apparatus of Chen et al. (U.S. 6,180,401) teaches the culturing of polypeptides by a batch reactor, which is connected to a cross-flow filtration unit that removes the produced cells and sends the retentate back to the bioreactor. The bioreactor of Larsen (U.S. 6,492,135) teaches a U-loop reactor that separates the cells to be harvested while monitoring the pH of the solution during the process. Condon et al. (U.S. 6,198,944) teaches developing

recombinant viruses through the use of a bioreactor and a cross-flow filtration unit for separating out the infected cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL L. HOBBS whose telephone number is (571)270-3724. The examiner can normally be reached on Monday-Thursday 7:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mikhail Kornnakov can be reached on (571) 272-1303. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MLH

/Michael Kornakov/

Supervisory Patent Examiner, Art Unit 4151